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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/633,698	08/05/2003	Conrad Padraig Quinn	1581.0770001	5476

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EXAMINER	
KAM, CHIH MIN	

ART UNIT	PAPER NUMBER
1656	

DATE MAILED: 05/09/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/633,698	QUINN ET AL.	
	Examiner	Art Unit	
	Chih-Min Kam	1656	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 February 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,4-8,11-15,18-21 and 55* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,4-8,11-15,18-21 and 55* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *05 August 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☒ Certified copies of the priority documents have been received in Application No. 09/763,669.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of the Claims

1. Claims 1, 4-8, 11-15, 18-21 and 55 are pending.

Applicants' amendments and Declaration of Dr. Keith Foster filed February 21, 2006 are acknowledged. Applicants' response and Declaration of Dr. Keith Foster have been fully considered. Claims 1, 8 and 15 have been amended, claims 2, 3, 9, 10, 16 and 17 have been cancelled, and a new claim 55 has been added. Therefore, claims 1, 4-8, 11-15, 18-21 and 55 are examined.

Withdrawn Claim Rejections- 35 USC § 112

2. The previous rejection of claims 2, 3, 9, 10, 16 and 17 under 35 U.S.C. 112, first paragraph, is withdrawn in view of applicant's cancellation of the claim in the amendment filed February 21, 2006.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claims 1, 4-8, 11-15, 18-21 and 55 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of treating hypersecretion of mucus, asthma and COPD, the method comprising administering topically to the airways of a patient in need thereof, a compound comprising a light chain (L-chain) or L-chain fragment of a clostridial neurotoxin containing the active proteolytic enzyme domain, a targeting domain that binds to a target cell of a mucus secreting cell or a neuronal cell controlling or directing mucus secretion,

and a translocating domain that translocates the L-chain or L-chain fragment into the target cell, wherein the translocating domain is a translocating domain of clostridial neurotoxin, with the proviso that the compound is not a botulinum toxin, does not reasonably provide enablement for a method of treating hypersecretion of mucus, asthma and COPD, administering topically to the airways of a patient in need thereof, a compound comprising a light chain (L-chain) or L-chain fragment of a clostridial neurotoxin containing the active proteolytic enzyme domain, a targeting domain that binds to a target cell of a mucus secreting cell or a neuronal cell controlling or directing mucus secretion, and a translocating domain that translocates the L-chain or L-chain fragment into the target cell, wherein the translocating domain is any translocating domain of a bacterial or viral protein, with the proviso that the compound is not a botulinum toxin. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Claims 1, 4-8, 11-15, 18-21 and 55 encompass a method of treating hypersecretion of mucus, asthma and COPD by administering to a patient in need thereof, a compound comprising a light chain (L-chain) or L-chain fragment of a clostridial neurotoxin, a targeting domain that binds to a target cell of a mucus secreting cell or a neuronal cell controlling or directing mucus secretion, and a translocating domain, wherein the translocating domain is a translocating domain of a bacterial or viral protein, with the proviso that the compound is not a botulinum toxin. The specification, however, only discloses cursory conclusions (pages 2-3) without data supporting the findings, which state that a compound comprising an inhibiting domain comprising a light chain of a clostridial neurotoxin or a active fragment or variant thereof, a

translocating domain that translocates the inhibiting domain into the cell, and a targeting domain that binds to a target cell of a mucus secreting cell or a neuronal cell controlling or directing mucus secretion, can be used to treat hypersecretion of mucus, asthma and COPD. There are no indicia that the present application enables the full scope in view of the use of a compound comprising the inhibiting domain, the targeting domain and the translocating domain in treating hypersecretion of mucus, asthma and COPD as discussed in the stated rejection. The present application does not provide sufficient teaching/guidance as to how the full scope of the claims is encompassed. The factors considered in determining whether undue experimentation is required, are summarized in In re Wands (858 F2d at 731,737, 8 USPQ2d at 1400,1404 (Fed. Cir.1988)). The factors most relevant to this rejection are the breadth of the claims, the absence or presence of working examples, the state of the prior art and relative skill of those in the art, the predictability or unpredictability of the art, the nature of the art, the amount of direction or guidance presented, and the amount of experimentation necessary.

(1). The breadth of the claims:

The breadth of the claims is broad and encompasses unspecified variants regarding the translocating domains in the compounds which are not adequately described or demonstrated in the specification.

(2). The absence or presence of working examples:

The specification describes the preparation of substance P-LH_N/A conjugate (Example 1); the preparation of a broad specificity agent WGA-LH_N/A (Example 2; WGA= wheat germ agglutinin); the use of WGA-LH_N/A in inhibiting neurotransmitter release from cultured neuronal cells (Example 3); a method for preparation of LC/B-$DT_{194-380}$-EGF (DT= diphtheria

toxin; Example 4), LC/B-$PE_{405-613}$-EGF (PE= pseudomonas exotoxin; Example 5), or LC/A-HA-EGF (HA= influenza virus haemagglutinin; Example 6). The specification demonstrates the inhibition of neurotransmitter release by WGA-LH_N/A in vitro (Example 3), however, there are no working examples indicating the claimed methods in association with the variants, e.g., compounds containing various translocating domains of bactertial or viral proteins.

(3). The state of the prior art and relative skill of those in the art:

The related art (e.g., Shone *et al.*, WO 98/07864) teaches a polypeptide which has the first domain and second domains obtained from a clostridial toxin, can be translocated into the target cell and cleave the plasma-membrane associated proteins essential to exocytosis due to the functions of two domains, and the polypeptide can also contain a third domain (e.g., the Hc domain of the native toxin could be replaced by a targeting domain) that targets to a specific cell, thus the polypeptide is useful in inhibition of exocytosis in target cell such as the neuronal cell; Aoki *et al.* (WO 95/17904) teach botulinum toxins are used to treat cholinergic controlled secretions such as excessive mucus secretion; and Sanders *et al.* (WO 95/28171) teach botulinum toxin is used to treat autonomic nerve dysfunction such as asthma and COPD. However, the general knowledge and level of the skill in the art do not supplement the omitted description, the specification needs to provide specific guidance on the use of the compounds containing various translocating domains of bactertial or viral proteins in the treatment of hypersecretion of mucus, asthma and COPD to be considered enabling for variants.

(4). The amount of direction or guidance presented and the quantity of experimentation necessary:

The claims are directed to a method of treating hypersecretion of mucus, asthma and COPD, comprising administering topically to the airways of a patient in need thereof, a compound comprising a light chain (L-chain) or L-chain fragment of a clostridial neurotoxin, a targeting domain that binds to a target cell, and a translocating domain that translocates the L-chain or L-chain fragment, wherein the translocating domain is a translocating domain of a bacterial or viral protein, with the proviso that the compound is not a botulinum toxin. The specification has demonstrated the inhibition of neurotransmitter release from cultured neuronal cells by WGA-LH_N/A (Example 3), it has not demonstrated the use of compounds containing various translocating domains of bacterial or viral proteins in treating hypersecretion of mucus, COPD and asthma, and there are no working examples indicating the claimed methods associated with the variants. Furthermore, the specification has not shown the effects of the compounds containing various translocating domains of bacterial or viral proteins in the treatment. Since the specification fails to provide sufficient guidance on the use of the compounds containing various translocating domains of bacterial or viral proteins in the treatment, it is necessary to carry out undue experimentation to use the compound and to assess the effect of the compound in the treatment.

(5). Predictability or unpredictability of the art:

The claims encompass a method of treating hypersecretion of mucus, COPD and asthma using the compounds comprising a light chain (L-chain) or L-chain fragment of a clostridial neurotoxin, a targeting domain that binds to a target cell, and a translocating domain that translocates the L-chain or L-chain fragment, however, the effects of the compounds containing various translocating domains of bacterial or viral proteins and the treating conditions for disease

are not sufficiently described in the specification, the effects of the compounds containing various translocating domains of bacterial or viral proteins in the treatment is unpredictable.

(6). Nature of the Invention

The scope of the claims includes a method of treating of hypersecretion of mucus, COPD and asthma using with a compound comprising a light chain (L-chain) or L-chain fragment of a clostridial neurotoxin, a targeting domain that binds to a target cell, and a translocating domain that translocates the L-chain or L-chain fragment, but the specification has not shown the effect of the compounds comprising various translocating domains of bacterial or viral proteins. Thus, the disclosure is not enabling for the reasons discussed above.

In summary, the scope of the claim is broad, while the working example does not demonstrate the claimed methods associated with the variants, and the guidance and the teaching in the specification are limited, therefore, it is necessary to have additional guidance and to carry out further experimentation to assess the outcome of the treatment using the compounds.

Response to Arguments

Applicants indicate claims 1, 8 and 15 have been amended to specify that the translocating domain is a translocating domain of a bacterial or viral protein, and claim 5 was previously amended to specify that the translocating domain is a translocating domain of a specific bacterial or viral proteins (see Table at page 8). Translocating domains suitable for use in the agents of the present invention have a common function in that they deliver the L-chain or L-chain fragment into the cell by a process of endocytosis (see specification, page 9, paragraph 0030), and suitable translocation domains may be obtained from a wide range of sources, in particular, microbial sources such as bacterial or viral sources (see specification, page 7,

paragraphs 0023-0024). The artisan skilled in the art, reading the present specification, would be able to identify suitable translocating domains for use in the present invention as a routine matter. By way of example, suitable methodologies are described in the specification (see pages 7-9, paragraphs 0027 to 0030). In particular, Shone, C. C. et al., Eur. J Biochem. 167: 175-180 (1987) and Blaustein, R. O. et al., FEBS Letters 226, 115-120 (1987) provide simple assays to identify bacterial translocating domains having the desired translocating activity without undue experimentation.

Declaration by Dr. Keith Foster (Exhibit A) states that microbial or viral translocating domains for use in the present invention can be routinely identified by the artisan skilled in the art.

Applicants further assert that the specification at pages 7-9 provides a detailed description of how to obtain and identify microbial or viral translocating domains for use in the present invention; Example 3 describes the inhibition of neurotransmitter release from cultured neuronal cells by a particular conjugate, WGA-LH_N/A, and Figures 4-6 clearly show the inhibiting effect of the WGA-LH_N/A conjugate on neurotransmitter release; The presence of additional working examples in the specification is not required for enablement of the invention. The specification need not contain an example if the invention is otherwise disclosed in such manner that one skilled in the art will be able to practice it without an undue amount of experimentation. Applicants further provide more experimental evidence to show that the compounds of the present invention have therapeutic activity (Annex 1 (Exhibit B); Figs 1-6 (Exhibit C)). Three new conjugates (i.e., LH_N/C-EGF; LH_N/B-EGF; LC/C-RGD-H_N/C) prepared in accordance with the present invention were tested for their ability to inhibit mucin release. These results confirm

that conjugates of the present invention correctly translocate into the target cells and block secretion of mucin from the cells and thus would be useful in the presently claimed methods of treating hypersecretion of mucus, COPD and asthma. Thus, a representative sample of the conjugates of the invention has been demonstrated to have therapeutic activity when tested in an art-accepted model of mucus secretion. Therefore, the artisan skilled in the art, reading the present specification, would be able to make and use the compounds comprising the translocating domains of the invention, without undue burden (pages 9-15 of the response).

Applicants' response and Declaration by Dr. Keith Foster have been considered, however, the arguments are not fully persuasive because of the following reasons. The specification has only demonstrated the in vitro effect of WGA-LH_N/A (Example 3), which contains a translocating domain of a clostridial toxin, the specification has not demonstrated the make/use of compounds containing a translocating domain from various bacterial or viral proteins in treating hypersecretion of mucus, COPD and asthma. Although the specification (at pages 7-9) indicates translocating domains suitable for use in the agents of the present invention have a common function in that they deliver the L-chain or L-chain fragment into the cell by a process of endocytosis, and provides a description of how to obtain and identify bacterial or viral translocating domains for use in the present invention (e.g., some known translocating domains, paragraph 0028) and the assays to identify bacterial translocating domains having the desired translocating activity (paragraph 0030; e.g., Shone et al. (1987) and Blaustein et al., (1987)), the specification has not demonstrated the effects of the translocating domains from various bacterial or viral proteins in the compounds containing an L chain of a chlostridial toxin and a targeting domain in the claimed methods except for WGA-LH_N/A. Regarding the three new conjugates

(i.e., LH_N/C-EGF; LH_N/B-EGF; LC/C-RGD-H_N/C), it has been shown that these conjugates translocate into the target cells and block secretion of mucin from the cells (Exhibits B-C), but these translocating domains are the translocating domain of clostridial toxins, which are enabled as indicated in paragraph 3 (see above). Thus only the compounds containing a translocating domain of a clostridial toxin that translocates the L-chain or L-chain fragment into the target cell in the claimed methods are enabled. For compounds containing various bacterial or viral translocating domains, it would require undue experimentation to make/use these compounds in the claimed methods and to show the effects of these compounds in the treatment. Therefore, the full scope of the claims are not enabled.

Conclusion

4. No claims are allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Chih-Min Kam whose telephone number is (571) 272-0948. The examiner can normally be reached on 8.00-4:30, Mon-Fri.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Kathleen Kerr can be reached at 571-272-0931. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Chih-Min Kam, Ph. D.
Patent Examiner

CHIH-MIN KAM
PATENT EXAMINER

CMK
May 6, 2006